Hot off the Press

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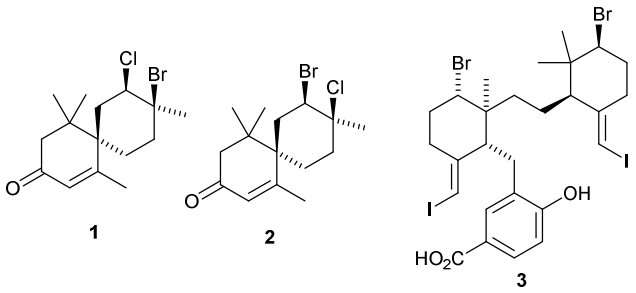
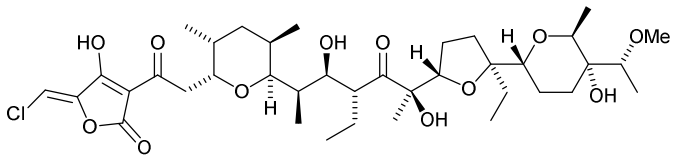
Abstract: A personal selection of 32 recent papers is presented covering various aspects of current developments in bioorganic chemistry and novel natural products such as macrophilone A from *Macrorhynchia philippina*.

A method for validating the structures of natural products by computed ^{13}C NMR chemical shifts of carbons bearing heavy atoms has been developed using a large number of halogenated natural products.[1] This technique, together with computed spin-spin coupling constants, has been used to revise the structure of 16 natural products such as tristichone C that was revised from **1** to **2**. Several iodinated meroterpenoids, including iodocallophycoic acid A **3**, have been isolated from a *Callophycus* sp.[2] Iodocallophycoic acid A **3**, showed moderate antibiotic activity against MRSA and VREF. A metabolite of a soil-derived *Actinomadura* sp., nonthmicin **4**, is a polyether polyketide with the first example of a natural chlorinated tetronic acid.[3]





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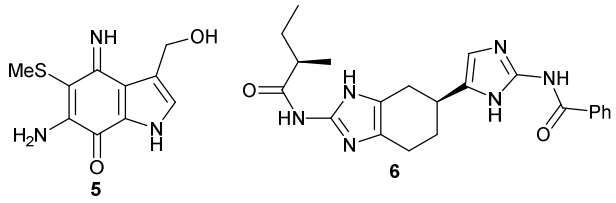
Macrophilone A **5** is a pyrroloiminoquinone from the stinging hydroid *Macrorhynchia philippina*.[4] The structure of macrophilone A **5** was predicted using long-range NMR correlations and DFT calculations and confirmed by synthesis. Terrazoanthine A **6**, from the zoantharian *Terrazoanthus onoi*, is a representative of a new structural class of 2-aminoimidazole alkaloids.[5] A biosynthetic pathway to terrazoanthine A **6**, involving a [4+2] cycloaddition, has been proposed. Meyeniin A **7**, from tubers of *Lepidium meyenii* (maca), is a novel sulfur-containing hexahydroimidazo[1,5-*c*]thiazole derivative.[6] The structure of meyeniin A **7** was confirmed by X-ray analysis and biomimetic synthesis. Macahydantoin A **8**, a thiohydantoin derivative with a new skeleton, was also isolated from *Lepidium meyenii*.[7] The structure of macahydantoin A **8** was confirmed by synthesis. The *C*-terminus peptide modification found in leupeptazin **9**, a metabolite of a *Streptomyces* sp., has not been found in nature before.[8] Leupeptazin **9** shows moderate inhibitory activity towards the collagenase cathepsin K.



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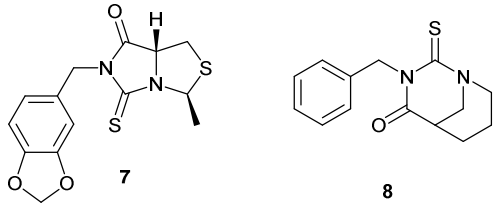

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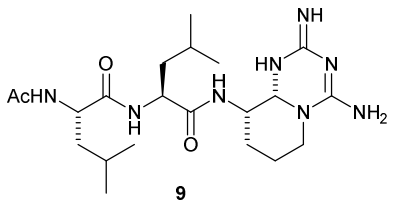

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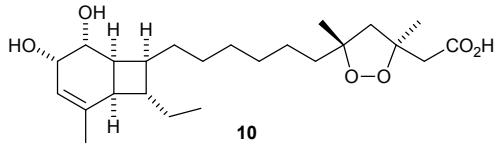
A sponge symbiotic association of *Plakortis halichondrioides* and *Xestospongia deweerdtae* is the source of an inseparable mixture of plakortinic acids A **10** and B **11** that have an unusual bicyclo[4.2.0]octane unit.[9] It is proposed that this ring system is formed from a linear tetraene precursor. The mixture of plakortinic acids A **10** and B **11** shows cytotoxic activity at submicromolar concentration. The structure of spiroaspertrione A **12**, a metabolite of an *Aspergillus* sp. with a novel terpene-polyketide skeleton, was confirmed by X-ray analysis.[10] A biosynthetic pathway to spiroaspertrione A **12**, involving its co-metabolite andiconin B **13**, has been proposed. Spiroaspertrione A **12** shows potent resensitisation of oxacillin against MRSA.



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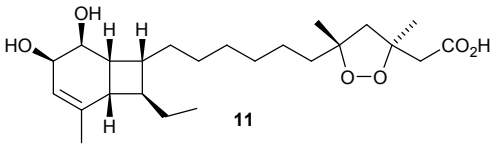

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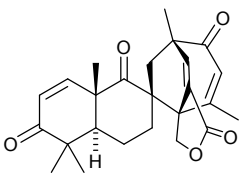

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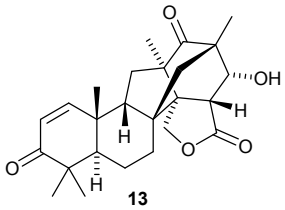

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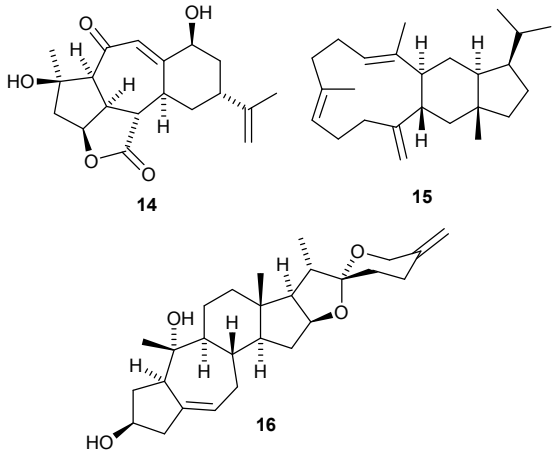
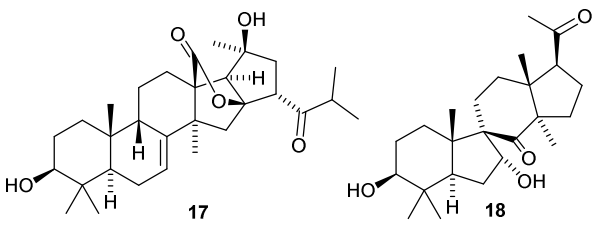
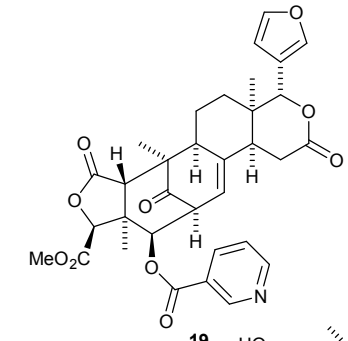
Fragilolide A **14**, from the gorgonian coral *Junceella fragilis*, has a new 18-norcembrane diterpenoid skeleton with 4,13 and 7,11 cyclisations.[11] Norcembranoids are often found in *Sinularia* species of soft corals. This is the first example of a norcembranoid from a gorgonian species. Expression of this gene in *E. coli* produced lydicene **15** that has a new diterpenoid skeleton. A sestertepene synthase has been

identified from the genome of *Arabidopsis thaliana* that produces the sesterterpenoid thalianatriene **15** which has a novel tricyclic skeleton.[12] A biosynthetic pathway to thalianatriene **15** has been proposed. The structure of bufospirostenin A **16**, from the toad *Bufo bufo gargarizans*, was confirmed by X-ray analysis.[13] Bufospirostenin A **16** is the first spirostanol to be found in animals.



Fallaxosides B_1 and D_3 are triterpenoid glycosides, from the sea cucumber *Cucumaria fallax*, with the novel aglycones **17** and **18**, respectively.[14] It is proposed that the skeleton of **17** is formed by aldol condensation of a 16,24-diketone precursor and that the skeleton of **18** is formed by a pinacol rearrangement of a 7,8-dihydroxy precursor. The structure of the limonoid triconoid A **19**, from *Trichilia connaroides*, was established by X-ray analysis.[15] The authors propose a biosynthetic pathway to the novel rearranged mexicanolide skeleton of triconoid A **19**. Belamcandanin A **20**, from rhizomes of *Belamcanda chinensis*, is the first example of an adduct of a spiroiridal triterpenoid with an isoflavonoid.[16]





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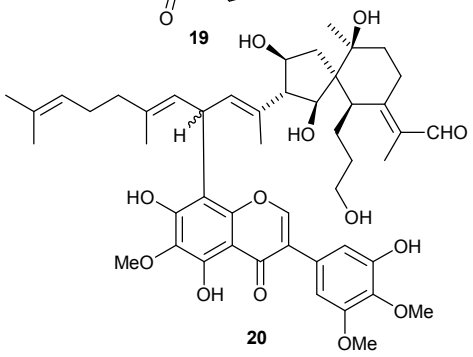

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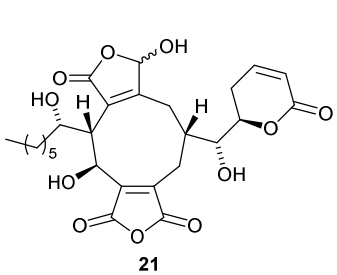
Through characterisation of the biosynthetic pathway of the fungal polyketide rubratoxin A **21**, the six redox enzymes involved in the key complexity-generating steps have been revealed.[17] These include α-ketoglutarate- and iron(II)-dependent dioxygenases that hydroxylate sp^3 carbons and, a flavin-dependent dehydrogenase that produces the unsaturated lactone. A β-ketoacyl-acyl carrier protein synthase III-like enzyme, PtmR has been shown to transfer a 6-methylsalicylyl moiety from an iterative type I polyketide synthase to an aminocyclopentitol unit during pactamycin (e.g. pactamycin A **22**) biosynthesis.[18] PtmR was found to accept a wide range of *S*-acyl-*N*-acetylcysteamines as substrates, resulting in the generation of a range of novel pactamycin derivatives.



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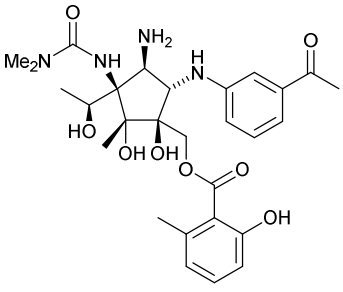

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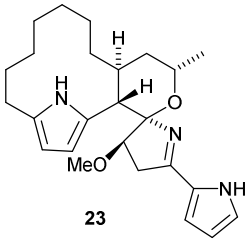
The final key stages of the biosynthesis of marineosins (e.g. marineosin A **23**) have been established with the identification of a novel bifunctional enzyme MarH, which was shown to catalyse condensation of 4-methoxy-2,2'-bipyrrole-5-carboxaldehyde with 2-undecylpyrrole, as well as hydroxylation of the alkyl side-chain of the resulting prodiginine.[19] Genome mining in bacteria and fungi using the EriG protein, a membrane-bound diterpene cyclase from *Hericium erinaceum* has led to the discovery of seven new diterpene cyclases.[20] Expression of the cyclases using an engineered *Escherichia coli* strain allowed characterisation of their products, including the new diterpene lydicene **24**, that possesses an unprecedented skeleton.



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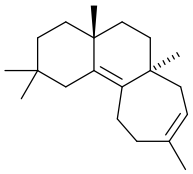
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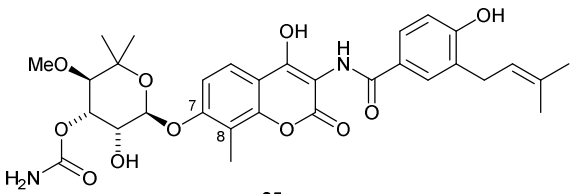
A detailed study of NovO, a C-methyltransferase that catalyses the regioselective C8-methylation of the coumarin component of the antibiotic novobiocin **25** in *Streptomyces spheroids* has identified the active site residues responsible for binding the substrate.[21] One of these residues, His120 was also shown to deprotonate the phenolic 7-hydroxyl, locking the substrate in position for the subsequent methyl transfer step. The products of a putative 2-hydroxyphenylthiazoline biosynthetic gene cluster from the genome of *Streptomyces venezuelae* ATCC 10712 include the known 2-hydroxyphenylthiazolines thiazostatin **26** and watasemycin **27**.[22] Gene deletion experiments identified a type B radical-SAM methylase homologue that methylates the thiazoline ring of thiazostatin during the final biosynthetic step to form watasemycin.



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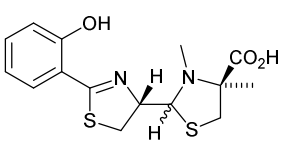

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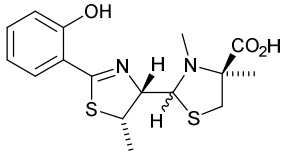

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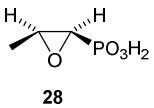
The last two steps of the biosynthesis of the broad-spectrum natural product antibiotic fosfomycin **28** have been characterised using a combination of in vitro activity reconstitution and crystallographic analysis of the enzymes involved.[23] The reductase Psf3 was shown to convert 2-oxopropylphosphonate to (*S*)-2-hydroxypropylphosphonate, which is then converted to fosfomycin by a Psf4-catalysed epoxidation. A genome-mining approach has led to a comprehensive understanding of the biosynthesis of lipopeptides in myxobacteria.[24] Identification of potential producer strains allowed the discovery and isolation of four novel lipopeptide core types (e.g. **29**).



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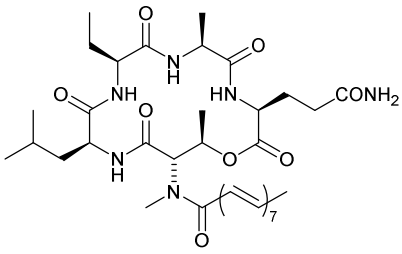

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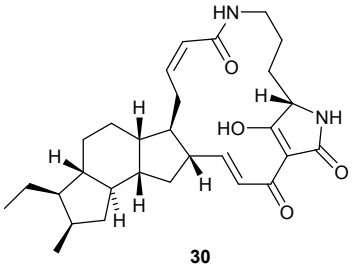
The biocatalytic total synthesis of the bacterial polycyclic tetramate ikarugamycin **30**, a compound which shows anti-leukemic and anti-inflammatory activity has been achieved using three recombinant enzymes, IkaABC.[25] The one-pot, three-enzyme process which uses acetyl-CoA, malonyl-CoA and L-ornithine building blocks allows the construction of 15 carbon-carbon and 2 carbon-nitrogen bonds and sets 8 stereogenic centres, yielding ikarugamycin in 9% overall yield. A biohybrid catalyst

composed of palladium(0) nanoparticles and a crosslinked network of aggregated lipase B from *Candida antarctica* have been used for a one-pot cascade process leading to the resolution of secondary alcohols.[26] The first stage of the process involves a palladium-catalysed cycloisomerisation of 4-pentynoic acid that produces a lactone that then acts as an acyl donor in the second stage lipase-catalysed kinetic resolution (Scheme 1).



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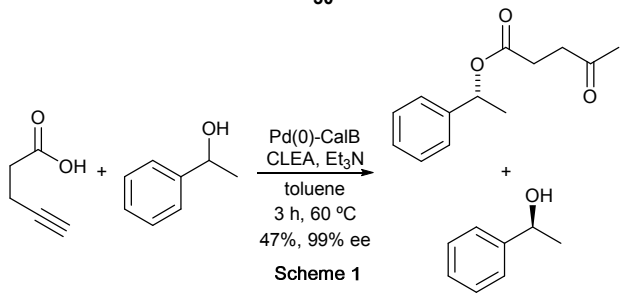
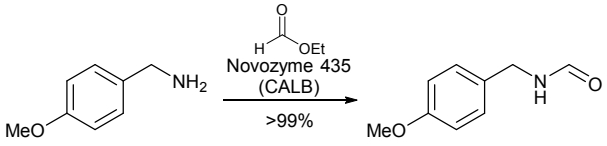
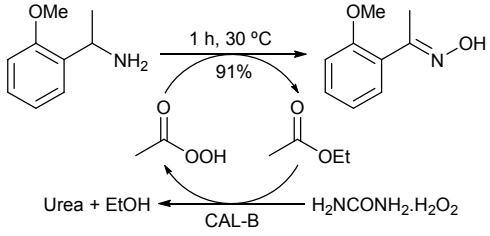


Scheme 1

The first example of a biocatalytic *N*-formylation of amines has been reported.[27] The process which uses Novozyme 435 (lipase B from *Candida antarctica*) and ethyl formate was shown to be general and scalable for a wide range of aliphatic and aryl amines (Scheme 2). A one-pot two-step conversion of amines to oximes has been developed using a lipase mediated perhydrolysis of ethyl acetate to generate a peracid, which then performs an oxidation to give the oxime (Scheme 3).[28] The optimal method utilised lipase B from *Candida antarctica* and gave the majority of products in excellent yields by a simple extraction protocol.

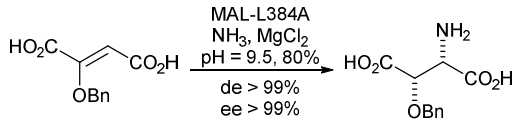


Scheme 2

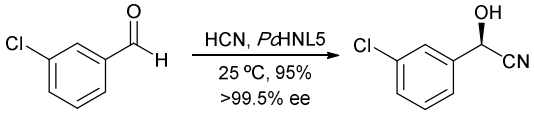


Scheme 3

An optimised, multi-gram scale chemoenzymatic synthesis of L-*threo*-3-benzyloxyaspartate **31** has been reported using methylaspartate ammonia lyase (MAL-384A).[29] Modifications such as the use of ammonia and high pH led to >98% conversion and 80% isolated yield of **31** (Scheme 4), which is used as a building block for the preparation of probes to study excitatory amino acid transporters. The cloning and overexpression of hydroxynitrile lyases from *Prunus communis* has led to the identification of *Pc*HNL5 as an excellent biocatalyst for asymmetric hydrocyanation.[30] The enzyme was found to convert a range of aromatic aldehydes to valuable chiral cyanohydrin building blocks in excellent yields and optical purities (Scheme 5).



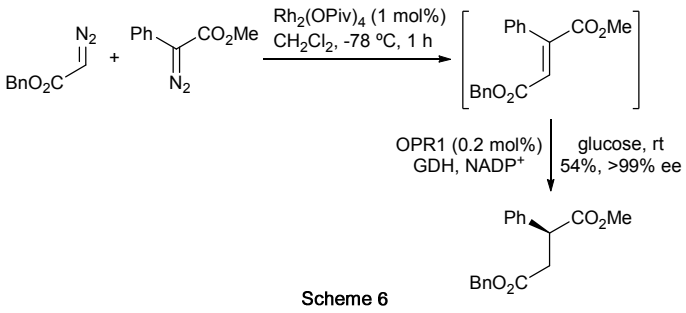
Scheme 4 **31**



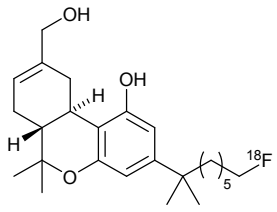
Scheme 5

A one-pot two-step asymmetric synthesis of 2-substituted succinate derivatives has been developed using a rhodium-catalysed diazocoupling, followed by an ene-reductase mediated reduction of the resulting *E*-alkene.[31] Screening a range of ene-

reductases identified OPR1 from *Lycopersicum esculentum* as effective for the reduction of substrates with bulky *tert*-butyl or benzyl esters (Scheme 6). New potential positron emission tomography (PET) tracers have been developed for the in vivo imaging of cannabinoid receptors (CB_1 and CB_2).[32] Fluorinated analogues of 11-hydroxy-Δ^8-tetrahydrocannabinol (e.g. **32**) were synthesised and shown to retain potent pharmacological properties. The authors propose that [^{18}F]**32** could be used for overall mapping of CB receptors or for selective blocking and competition experiments.



Scheme 6



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